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The Contribution of Malglycemia to Mortality among Allogeneic Hematopoietic Cell Transplant Recipients

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Allogeneic hematopoietic cell transplantation (HCT) continues to be associated with substantial rates of nonrelapse mortality (NRM). Numerous factors influence glucose metabolism among HCT recipients. We hypothesized that "malglycemia," defined as hyperglycemia, hypoglycemia or increased glycemic variability, is associated with increased mortality in HCT patients. In a retrospective cohort study Cox regression was used to assess the association of malglycemia after transplant with day 200 NRM. A total of 66,062 blood glucose (BG) measurements from 1175 adult allogeneic HCT recipients between 2000 and 2005 at the Fred Hutchinson Cancer Research Center were evaluated (median 0.55 values per patient-day, range: 0.09-3.62). Overall, there were 215 cases of NRM by day 200 post-HCT and 601 deaths from any cause throughout observation. After adjustment for previously identified factors associated with NRM, all 3 components of malglycemia were associated with increased NRM when individually modeled as time-dependent covariates. Specifically, the hazard ratio for death was 1.93 for BG >200 mg/dL ($P = .0009$) and 2.78 for BG >300 ($P = .0004$) compared with BG 101-150 mg/dL. A minimum BG ≤89 was associated with a risk of day 200 NRM 2.17 times that of a minimum BG >89 ($P < .0001$). The upper quartile of glucose variability was associated with a 14.57-fold increase in risk of NRM by day 200 relative to the first quartile ($P < .0001$). These retrospective data indicate that malglycemia is associated with mortality following HCT. The applicability of these findings to other situations and whether correcting malglycemia in HCT can lead to reductions in mortality remain to be determined.

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INTRODUCTION

Disordered glucose metabolism is associated with increased risk of death among persons with both chronic and acute medical illnesses [1-3]. Recently, efforts have been made to control hyperglycemia during inpatient hospitalization, but results from clinical trials and retrospective analyses have demonstrated inconsistent findings with intensive insulin therapy [2-4]. The first prospective, randomized control trial in critically ill surgery patients reported a 42% reduction in mortality [2], but these results were not replicated in the same group's second study of critically ill medical patients [5]. Other populations studied in randomized control trials including those with acute myocardial infarction [6,7], and more recently severe sepsis [8], have not shown improvements with intensive insulin therapy. Conversely, other retrospective data have suggested benefits from improved glucose control in the hospital [9,10].

There is also growing evidence that hypoglycemia may have a profound detrimental effect on outcomes, including death and length of stay, thus limiting the efforts for meticulous glucose control in the hospital [11]. Besides the known neuroglycopenic dangers of seizures and coma, the data suggest that rates of "severe hypoglycemia" (often defined in this literature as a blood glucose less than 40 mg/dL) approximate 18% in a research setting [5,8]. Whether this is a marker of

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poor outcome or offsets any benefit from intensive insulin therapy is unknown.

Glycemic variability, a measurement of glucose instability, was recently shown to be a predictor of mortality in critically ill patients [12]. There has also been increased interest in evaluating the impact of glycemic variability on the vascular outcomes of diabetes [13]. It appears that oxidative stress is generated by variable glucose levels [14] but at this time the role of this process in the pathogenesis of micro- and macroangiopathy is unclear.

Despite impressive gains in the safety of HCT over the last 20 years, nonrelapse mortality (NRM) remains high. Major causes of NRM include infection, organ toxicity, and graft-versus-host disease (GVHD). Under the best of circumstances, NRM occurs in 10% to 15% of HCT patients by 100 days and in 20% to 30% of patients by 2 to 3 years [15,16], and it is therefore important to identify modifiable factors that could further reduce NRM. In contrast to critically ill patient groups, little data exist regarding the relative contribution of the components of malglycemia, which we define as disordered glucose metabolism consisting of hyperglycemia, hypoglycemia, or increased glycemic variability, to infections or mortality posttransplant.

Allogeneic HCT provides a novel setting in which to examine the association between malglycemia and outcome, as the population consists of patients who are of closely monitored and expected to have a high incidence of hyperglycemia, infections, and mortality posttransplant. In this retrospective study, we examined the association between disordered glucose metabolism and the post-HCT outcomes of infection and death among a cohort of 1175 patients who underwent allogeneic HCT at a single transplant center.

METHODS

Patients

All patients 18 years of age and older undergoing allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC), Seattle, Washington, were approached for participation in a study protocol that allows for retrospective review of medical records; $>$ 90% of patients gave their consent. All patients who consented and were undergoing their first HCT between 2000 and 2005 who had $\geq$1 glucose measurement between day 0 (time of receipt of stem cells) and day 100 were included. This study received approval by the FHCRC institutional review board.

Evaluation and Outcomes

Data including basic demographic characteristics, details of HCT, and any available measurements of blood glucose (BG, serum or plasma) level were abstracted from the FHCRC HCT database. Bedside capillary glucose values were not used in this analysis. Serum and plasma glucose concentrations were determined using the central laboratory's Beckman-Coulter Synchron LX-20 automated chemistry analyzer. Information on infections was obtained from 3 sources. All bacteremias were identified through electronic records from the microbiology laboratory. Data on cytomegalovirus reactivation and disease [17], invasive fungal infections [18] and Gram-negative bacteremias [19] were obtained through previously validated databases.

Statistical Analysis

Cox regression was used to assess the association between BG and outcome following HCT. Five glycemic parameters were examined: individual BG values, glycemic variability (measured by the standard deviation of individual BG values), average BG value, minimum BG value, and maximum BG value. BG values between days 0 and 100 following HCT were considered, as this is a time period during which regular BG measurements are taken because of the fact that patients remain in the FHCRC system and are closely monitored during this time window. Outcomes included day 200 nonrelapse mortality (NRM), overall mortality (OM), and fungal infection, cytomegalovirus (CMV) disease, and Gram-negative infections by day 130 post-HCT. Day 130 was chosen to allow a 30-day incubation period for infection acquired by day 100. For infections that could occur multiple times in a given patient, an Andersen-Gill model was fit [20]. Unless otherwise specified, all models were adjusted for severity of disease (low, intermediate, and high) [21], patient age at HCT, type of donor (HLA-identical sibling versus alternate donors [unrelated, mismatched sibling, or nonsibling relative]), year of transplant, and presence of grades 2-4 graft-versus-host disease [22] (GVHD, modeled as a time-dependent covariate). We consider GVHD (a post-HCT factor) because its occurrence is associated with increased NRM, and GVHD is treated with steroids, which increases BG. Each glycemic parameter was treated as a time-dependent covariate and modeled as a continuous variable using a cubic spline with 5 knots set (prior to data analysis) at the 5th, 25th, 50th, 75th, and 95th percentiles [23]. Ninety-five percent confidence intervals for the point estimates of hazard ratios were estimated from the observed variance/covariance matrix. In addition, each parameter was modeled as a categoric variable. All reported *P*-values are 2-sided. Those comparing nested regression models were derived from the likelihood-ratio test (LRT), and *P*-values from regression models were estimated from the Wald test. No adjustments were made for multiple comparisons.

RESULTS

Patients and Distribution of Glycemic Measurements

The population examined consisted of 1175 adult patients who received a first allogeneic HCT between 2000 and 2005 at the FHCRC. Patient characteristics are shown in Table 1.

There were a total of 66,062 BG measurements within 100 days following HCT. Descriptive statistics from these measurements are summarized in Table 1. Ninety-nine percent of patients had, on average, at least 1 BG measurement every 4 days. One thousand ninety-six patients (93%) were hyperglycemic (BG > 150 mg/dL) at least once over the course of observation. Additionally, 16% of patients (n = 190) were hypoglycemic (BG ≤70 mg/dL) at least once. Figure 1 shows the distribution of all BG measurements taken across all patients.

Table 1. Patient Characteristics and Blood Glucose Descriptive Statistics

Characteristic	N (percent of range)
Median age in years (range)	47.3 (18.0, 74.5)
Diagnosis	
CML	185 (16%)
AML	434 (37%)
ALL	105 (9%)
MDS	269 (23%)
NHL	72 (6%)
CLL	33 (3%)
AA	23 (2%)
Other	54 (5%)
Severity of disease	
Low	121 (10%)
Intermediate	438 (37%)
High	616 (52%)
Patient/donor CMV	
Donor +/Recipient +	342 (29%)
+/−	311 (27%)
−/+	152 (13%)
−/−	368 (31%)
Unknown	2 (0.17%)
Year of transplant	
2000	209 (18%)
2001	171 (15%)
2002	185 (16%)
2003	204 (17%)
2004	210 (18%)
2005	196 (17%)
Conditioning	
Ablative	943 (82%)
Nonablative	232 (18%)
GVHD prophylaxis	
CSP, MTX	553 (47%)
Other	622 (53%)
Median number BG measurements per patient (range)	52 (9, 227)
Median average BG per patient (range)	133 mg/dL (90, 284)
Median maximum BG per patient (range)	244 mg/dL (112, 1159)
Median minimum BG per patient (range)	83 mg/dL (26, 155)
Median standard deviation of BG values per patient (range)	33.2 mg/dL (6.8, 143.7)

CML indicates chronic myeloid leukemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; AA, aplastic anemia; CMV, cytomegalovirus; CSP, cyclosporine; MTX, methotrexate; GVHD, graft-versus-host disease; BG, blood glucose.

Mortality as a Function of BG Parameters

Shown in Table 2 are correlation coefficients for each of the possible pairs of glycemic parameters considered. Given these correlations, in regression models that consider more than 1 glycemic parameter we did not consider either maximum or average BG if glycemic variability was included. A total of 215 nonrelapse deaths occurred by day 200. When considered alone, each glycemic parameter was associated with a statistically significantly increased risk of day 200 NRM (Table 2).

Each parameter including individual BG, minimum BG, and glycemic variability, was significantly associated with NRM in a model considering all 3 with each modeled continuously. We found a nonmonotonic association between individual BG values and NRM, with hypoglycemia, hyperglycemia, and glycemic variability all associated with an elevated hazard of NRM (Figure 2a), although the association for BG values below 103 mg/dL was not statistically significant relative to this value, as evidenced by the 95% confidence intervals (a BG of 103 mg/dL is the value at which the modeled hazard of day 200 NRM reached a minimum).

We also modeled the 3 glycemic parameters as categoric variables. As shown in Table 3, glucose values >200 mg/dL were associated with an approximately 2- or more fold increased risk of nonrelapse death compared to values 101-150 mg/dL after consideration of glycemic variability, minimum BG, and the nonglycemic variables indicated ($P < .001$). Moreover, a minimum BG <90 mg/dL (89 mg/dL was the median minimum BG) was associated with a more than 2-fold risk of NRM compared to a minimum BG of 90 mg/dL or more ($P < .0001$). Even more striking, the risk of death was up to 14-fold higher among patients with the greatest variability in their BG measurements (the upper quartile of standard deviations) compared to patients with lower variability (the first quartile of standard deviations) ($P < .0001$).

Virtually all patients who develop clinically significant grades 2-4 acute GVHD (aGVHD) receive steroids for treatment of GVHD, whereas it is rare for patients who do not develop GVHD to receive steroids. Because steroid use leads to increased BG, we examined the impact of grades 2-4 aGVHD on the association of individual BG values with day 200 NRM. There was little suggestion that this association was dependent on the presence of grades 2-4 GVHD ($P = .81$, interaction test). Out of concern that BG values in close proximity to death could be abnormal as a result of the impending death (reduced hepatic and renal gluconeogenesis), we also fit models that excluded BG values that occurred within 2 days of

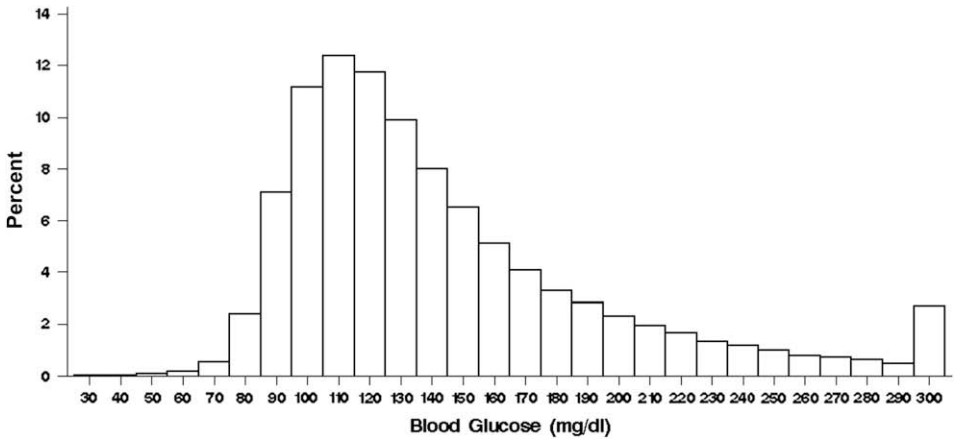

Figure 1. Distribution of BG values across all patients from days 0-100. Values <30 and >300 are assigned values of 30 and 300, respectively, for plotting purposes.

death. The qualitative conclusions reported above were unchanged (data not shown). In addition, the association between variability and NRM appeared to hold across all individual BG levels as well as minimum BG values ($P = .93$, $P = .22$, respectively in interaction tests).

There were 601 deaths from any cause over the course of observation (range: 8-2365 days [0.02-6.5 years]). Of the 574 survivors at last contact, the median follow-up was day 1471 (4.0 years), range of 97-2741 days (0.3-7.5 years). The same qualitative conclusions observed with day 200 NRM were seen with overall mortality (Table 4).

Infections as a Function of BG and Glycemic Variability

Although there could be many explanations for the observed association between malglycemia and post-transplant mortality, infections are a common complication in both diabetes and HCT, and we therefore sought to determine the relationship between malglycemia and infection in HCT. FHCRC has developed a database for invasive fungal infection, CMV disease, and Gram-negative bacteremias, which are the leading infectious complications in HCT. Combining these infections into a composite infection endpoint, there were 1073 episodes observed among 506 patients (43%) who had at least 1 occurrence. Of these 506, 235 (46.4%) had a single episode, 112 (22.1%) patients had 2, 61 (12.1%) had 3, and 80 (15.8%) had 4 or more episodes. Each glycemic parameter was significantly associated with infection rate in separate regression models ($P < .0001$ for each parameter) and in a model that includes individual BG, minimum BG, and glycemic variability ($P < .0001$ for each parameter) (Table 5). Shown in Figure 2b, i-iii, are hazard ratios (HR) of this composite infection endpoint as a function of each of these parameters, each plot adjusting for the 2 parameters other than the 1 depicted in the graph. As with NRM, the risk of infection was greatest among those with the most variable BG, greater than 2-fold higher when compared with those with the least variation in BG measurements ($P < .001$) (Table 5).

DISCUSSION

Few studies have examined the association between glucose and hematopoietic stem cell outcomes [24]. To our knowledge, this is the first report of glycemic variability impacting mortality or infection in

Table 2. Association of Glycemic Parameters with Day 200 NonRelapse Mortality and Correlation between Glycemic Parameters

		Correlation between Glycemic Parameters				
Glycemic Parameter	Statistical Significanceof Association with Day 200 NRM*	Individual BG Value	Average BG Value	Glycemic Variability	Minimum BG	Maximum BG
Individual BG value	$P < .0001$	—	R = 0.56	R = 0.46	R = 0.21	R = 0.38
Average BG value	$P < .0001$		—	R = 0.77	R = 0.29	R = 0.69
Glycemic variability	$P < .0001$			—	R = 0.09	R = −0.09
Minimum BG	$P < .0001$				—	R = −0.08
Maximum BG	$P < .0001$					—

BG indicates blood glucose; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant.
*Modeled as a continuous variable using a cubic spline, with *P*-value estimated from the likelihood ratio test. Each parameter is included in a separate regression model adjusting for disease, age, type of donor, year of HCT, and acute GvHD.

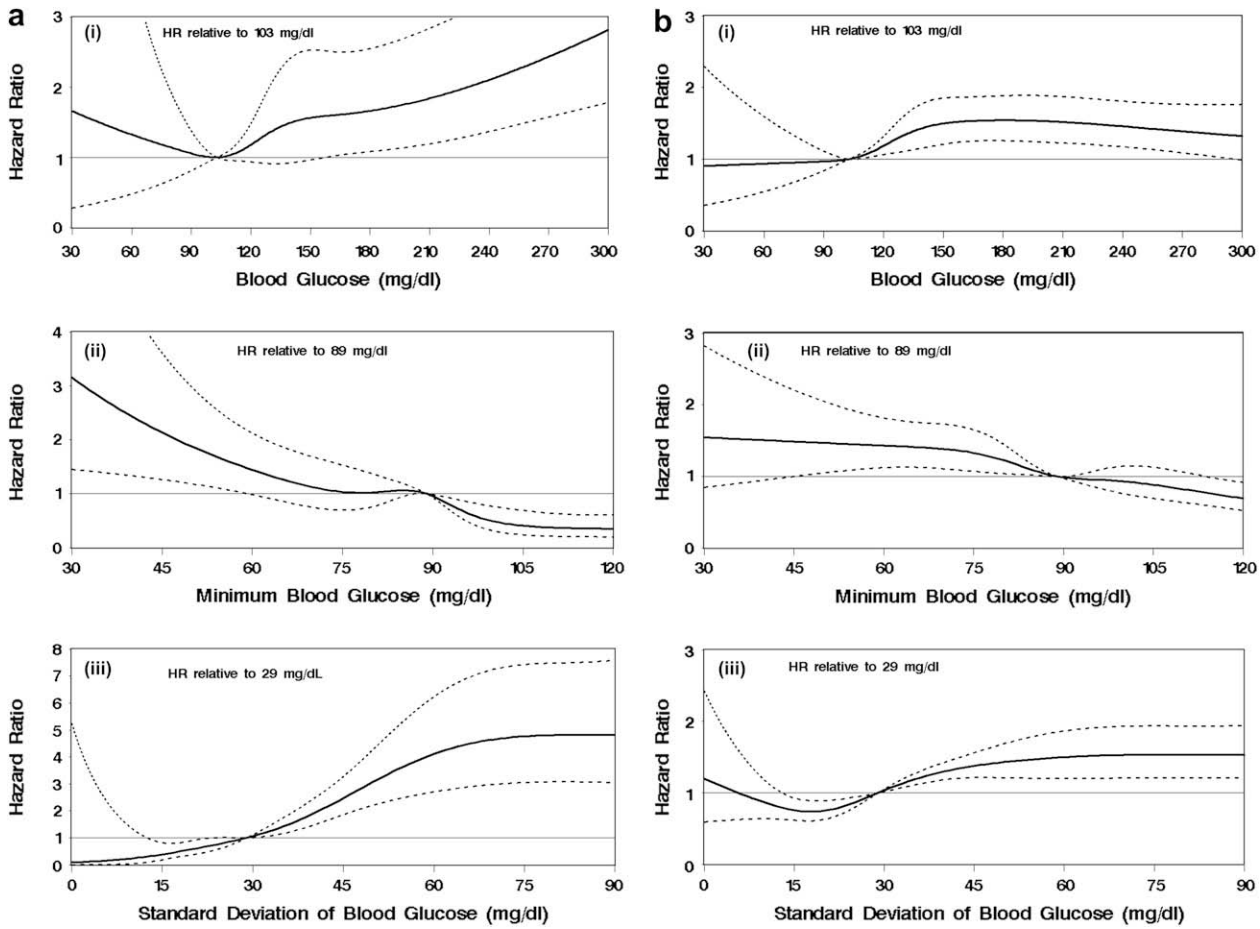

Figure 2. (a) Relationships between malglycemia and day 200 NRM. (i) HR of day 200 NRM as a function of BG relative to a value of 103 mg/dL (where the hazard of NRM attains its minimum) after adjusting for glycemic variability and minimum BG. (ii) HR of day 200 NRM as a function of minimum BG relative to a value of 90 mg/dL (the median minimum value) after adjusting for glycemic variability and individual BG value. Solid line represents the HR, dotted lines represent point-wise 95% confidence limits. (iii) HR of day 200 NRM as a function of glycemic variability (measured as the standard deviation) relative to a value of 29 mg/dL (the median standard deviation) after adjusting for individual and minimum BG values. (b) Relationship between malglycemia and composite infection endpoint. (i) HR of failure for the composite infection endpoint as a function of BG relative to a value of 103 mg/dL after adjusting for glycemic variability and minimum BG. (ii) HR of day 200 NRM as a function of minimum BG relative to a value of 90 mg/dL (the median minimum value) after adjusting for glycemic variability and individual BG value. Solid line represents the HR, dotted lines represent point-wise 95% confidence limits. (iii) HR of day 200 NRM as a function of glycemic variability (measured as the standard deviation) relative to a value of 29 mg/dL (the median standard deviation) after adjusting for individual and minimum BG values. Solid line represents the HR, dotted lines represent point-wise 95% confidence limits.

HCT patients. Because the term dysglycemia often refers to the spectrum of postprandial hyperglycemia above normal but not yet over the threshold considered diabetes [25], we define the overall dysregulation of glucose as "malglycemia." This term includes all 3 components of glycemic abnormalities noted in this study: hyperglycemia, hypoglycemia, and glucose variability.

In our cohort of patients undergoing allogeneic HCT, we found that all components of malglycemia were associated with death. Hyperglycemia has been associated with increased mortality in a number of different settings, including cardiovascular surgery in patients with diabetes [26] and critically ill trauma patients [27]. Several mechanisms for this have been postulated through the use of intensive insulin therapy, which leads to a reduction of inflammation [28], an improvement in circulating lipid levels which could have a direct effect on outcome [29], and by protecting the endothelium by inhibition of excessive inducible nitric oxide synthase [30].

Hyperglycemia also impairs immune function at both cellular and humoral levels with stunting of granulocyte function [31], dysfunctional cell signaling (evidenced by perturbations in the expression of proinflammatory cytokines), and suboptimal antibody generation [31-34]. Future analyses will need to determine whether hyperglycemia impacts cancer relapse or secondary malignancies in HCT recipients.

The mechanisms by which hypoglycemia might lead to an increased risk of death are less clear. Krinsley and Grover reported in a case-control study of over 5300 patients that even 1 episode of BG below 40 mg/dL was an independent risk factor for death [4].

Table 3. Relationship between Hyperglycemia, Glycemic Variability, Hypoglycemia and Day 200 NonRelapse Mortality after Hematopoietic Cell Transplant

Glycemic Parameter	Hazard Ratio*	95% Confidence Interval	*P*-Value
Blood glucose value (mg/dL)			
101-150	1 [reference]	—	—
0-70	2.40	0.87-6.66	.09
71-100	0.67	0.41-1.11	.12
151-200	1.39	0.96-2.00	.08
201-300	1.93	1.31-2.83	.0009
>300	2.78	1.58-4.92	.0004
Standard deviation of blood glucose values (mg/dL)			
0-18	1 [reference]	—	—
18-29	2.28	1.03-5.09	.04
29-49	4.83	2.22-10.50	<.0001
>49	14.57	6.83-31.06	<.0001
Minimum blood glucose (mg/dL)			
>89	1 [reference]	—	—
0-89	2.17	1.59-3.03	<.0001

*Hazard ratio derived from a multivariable model with exposure variables defined categorically and adjusted for the following predictors: severity of disease, patient age at hematopoietic cell transplant (HCT), type of donor, year of HCT, presence of grades 2-4 acute graft-versus-host disease.

Table 5. Relationship between Hyperglycemia, Glycemic Variability, Hypoglycemia and the Composite Infection Endpoint after Hematopoietic Cell Transplant

Glycemic Parameter	Hazard Ratio*	95% Confidence Interval	P-value
Blood glucose value (mg/dL)			
101-150	1 [reference]	—	—
0-70	1.30	0.65-2.60	.47
71-100	0.71	0.57-0.89	.002
151-200	1.29	1.08-1.54	.004
201-300	1.02	0.81-1.30	.85
>300	0.90	0.57-1.43	.66
Standard deviation of blood glucose values (mg/dL)			
0-18	1 [reference]	—	—
18-29	1.15	0.90-1.46	.26
29-49	1.59	1.24-2.04	.0002
>49	2.03	1.57-2.64	<.0001
Minimum blood glucose (mg/dL)			
0-89	1 [reference]	—	—
>89	1.41	1.20-1.67	<.0001

*Hazard ratio derived from a multivariable model with exposure variables defined categorically and adjusted for the following predictors: severity of disease, patient age at hematopoietic cell transplant (HCT), type of donor, year of HCT, presence of grades 2-4 acute graft-versus-host disease.

Hypoglycemia may frequently be a complication of severe sepsis [5,8], and Brunkhorst et al [8] recently reported that with intensive insulin therapy in a population with severe sepsis, severe hypoglycemia was more frequent, often life-threatening, and required prolonged hospitalizations. However, to our knowledge, no study to date has reported hypoglycemia as a risk factor for incident infection and there are certainly additional ways by which hypoglycemia could lead to death apart from infection. Although individual BG values <103 mg/dL were associated with an increased risk of day 200 NRM compared to BG values at this level, the association was not statistically significant (Figure 2a, i; the categoric modeling led to a similar conclusion). However, our data also showed that as the minimum BG achieved decreases, the hazard of day 200 NRM increases, and in fact, relative to the value of 89 mg/dL our model showed statistically significant increases for values below roughly 60 mg/dL (Figure 2a, iii). These data suggest that transplant patients may have an overall poor tolerance to hypoglycemia. The potential benefits of improved glucose control, therefore, might very well need to be balanced against the risk of hypoglycemia.

Table 4. Relationship between Hyperglycemia, Glycemic Variability, Hypoglycemia, and Overall Mortality after Hematopoietic Cell Transplant

Glycemic Parameter	Hazard Ratio*	95% Confidence Interval	*P*-value
Blood glucose value (mg/dL)			
101-150	1 [reference]	—	—
0-70	1.84	0.86-3.93	.12
71-100	0.78	0.62-0.99	.04
151-200	1.17	0.93-1.46	.17
201-300	1.69	1.29-2.22	.0002
>300	2.44	1.60-3.72	<.0001
Standard eeviation of blood glucose values (mg/dL)			
0-18	1 [reference]	—	—
18-29	1.22	1.03-5.09	.19
29-49	1.53	2.22-10.50	.007
>49	2.63	6.83-31.06	<.0001
Minimum blood glucose (mg/dL)			
>89	1 [reference]	—	—
0-89	1.58	1.31-1.92	<.0001

*Hazard ratio derived from a multivariable model with exposure variables defined categorically and adjusted for the following predictors: severity of disease, patient age at hematopoietic cell transplant (HCT), type of donor, year of HCT, presence of grades 2-4 acute graft-versus-host disease.

Glucose variability has just recently been described as a factor associated with morbidity and mortality among persons with disordered glucose metabolism. We found glucose variability to be strongly associated with death and infection, and it had a larger impact on the appropriate regression models than did individual BG value or minimum BG value. Our results are in agreement with Egi et al. [12], who reported a similar contribution of glucose variability on mortality in critically ill patients. It is difficult to differentiate the biologic impact of hyperglycemia from glucose variability, because hyperglycemia is strongly correlated with variability (in fact, in our data the correlation coefficient between the maximum BG attained throughout observation and the standard deviation of BG values throughout observation was 0.92). Furthermore, variability of glucose is usually a sign of insulin deficiency, which in turn, would require the providers of these patients to replace more insulin, leading to a greater risk of hypoglycemia. A major limitation of this retrospective study is that we were not able to measure insulin levels nor were we able to document individual episodes of iatrogenic hypoglycemia from administered insulin. However, it could be

speculated that even without attaining hypoglycemic levels, wide fluctuations in plasma glucose may result in oxidative stress as one possible mechanism. In the long term, this may lead to the vascular complications of diabetes [13,35], but the ramifications of this oxidative stress over shorter periods of hospitalization are unknown.

This study had a number of other limitations. First, as a nonrandomized retrospective study, data analyses were based on abstracted medical records. The timing and frequency of glucose measurements may have varied by either the degree of patient illness, history of malglycemia, or other unmeasured factors. The etiologies of patient malglycemia can only be speculated and there may be information bias. Most importantly, we had no information about whether patients had a history of diabetes mellitus or received insulin or oral hypoglycemic agents. Many factors are associated with mortality in HCT. Our models included those that have been identified in previous studies at FHCRC and elsewhere, but other factors may have been overlooked. Because of these limitations, although the data quite clearly show an association between malglycemia and outcome, we do not definitively know if the observed association is causal or if malglycemia is a surrogate for something that we were not able to measure, or if the observed malglycemia was because of more or less frequent monitoring.

Our study raises a number of difficult questions, paramount of which is the degree to which the level of BG should be controlled among HCT patients. Although the potential for hypoglycemia is concerning with the institution of tight glycemic control, the judicious use of insulin analogues [36] and the development of real-time continuous glucose sensors [37] would appear to make meticulous control in these patients an achievable goal for the immediate future.

We conclude that malglycemia is associated with both mortality and infection in the setting of HCT. Relatively small increases and decreases in normal glucose values appear to have a detrimental impact on these outcomes. Given the limitations of the current study cited above and the adverse outcomes reported in some of the recent trials [8], however, definitive proof of this association and whether correction of malglycemia leads to improved outcome can only be addressed with a randomized clinical trial. The mechanisms of how glucose itself and glucose variability might contribute to outcomes in this population require further study.

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